General

Guideline Title

Ovarian cancer. The recognition and initial management of ovarian cancer.

Bibliographic Source(s)

National Collaborating Centre for Cancer. Ovarian cancer. The recognition and initial management of ovarian cancer. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011 Apr. 28 p. (Clinical guideline; no. 122).

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre for Cancer on behalf of the National Institute for Health and Clinical Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Detection in Primary Care

Recommendations in this section update and replace recommendation 1.7.4 in Referral guidelines for suspected cancer (NICE clinical guideline 27).

Awareness of Symptoms and Signs

Refer the woman urgently if physical examination identifies ascites and/or a pelvic or abdominal mass (which is not obviously uterine fibroids) (see also Referral guidelines for suspected cancer [NICE clinical guideline 27]).

Carry out tests in primary care if a woman (especially if 50 or over) reports having any of the following symptoms on a persistent or frequent basis – particularly more than 12 times per month (see also Referral guidelines for suspected cancer [NICE clinical guideline 27]):

- Persistent abdominal distension (women often refer to this as 'bloating')
- Feeling full (early satiety) and/or loss of appetite
- Pelvic or abdominal pain
- Increased urinary urgency and/or frequency

Consider carrying out tests in primary care if a woman reports unexplained weight loss, fatigue, or changes in bowel habit.

Advise any woman who is not suspected of having ovarian cancer to return to her general practitioner (GP) if her symptoms become more frequent and/or persistent.

Carry out appropriate tests for ovarian cancer in any woman of 50 or over who has experienced symptoms within the last 12 months that suggest irritable bowel syndrome (IBS) (see the NGC summary of 'Irritable bowel syndrome in adults' [NICE clinical guideline 61]), because IBS rarely presents for the first time in women of this age.

Asking the Right Question – First Tests

Measure serum cancer antigen 125 (CA125) in primary care in women with symptoms that suggest ovarian cancer.

If serum CA125 is 35 IU/ml or greater, arrange an ultrasound scan of the abdomen and pelvis.

If the ultrasound suggests ovarian cancer, refer the woman urgently for further investigation (see also Referral guidelines for suspected cancer [NICE clinical guideline 27]).

For any woman who has normal serum CA125 (less than 35 IU/ml), or CA125 of 35 IU/ml or greater but a normal ultrasound:

- Assess her carefully for other clinical causes of her symptoms and investigate if appropriate.
- If no other clinical cause is apparent, advise her to return to her GP if her symptoms become more frequent and/or persistent.

Establishing the Diagnosis in Secondary Care

Tumour Markers: Which to Use?

Measure serum CA125 in secondary care in all women with suspected ovarian cancer, if this has not already been done in primary care.

In women under 40 with suspected ovarian cancer, measure levels of alpha fetoprotein (AFP) and beta human chorionic gonadotrophin (beta-hCG) as well as serum CA125, to identify women who may not have epithelial ovarian cancer.

Malignancy Indices

Calculate a risk of malignancy index I (RMI I) score (after performing an ultrasound) and refer all women with an RMI I score of 250 or greater to a specialist multidisciplinary team. See Appendix D in the original guideline document for details of how to calculate an RMI I score.

Imaging in the Diagnostic Pathway: Which Procedures?

Perform an ultrasound of the abdomen and pelvis as the first imaging test in secondary care for women with suspected ovarian cancer, if this has not already been done in primary care.

If the ultrasound, serum CA125 and clinical status suggest ovarian cancer, perform a computed tomography (CT) scan of the pelvis and abdomen to establish the extent of disease. Include the thorax if clinically indicated.

Do not use magnetic resonance imaging (MRI) routinely for assessing women with suspected ovarian cancer.

Tissue Diagnosis

Requirement for Tissue Diagnosis

If offering cytotoxic chemotherapy to women with suspected advanced ovarian cancer, first obtain a confirmed tissue diagnosis by histology (or by cytology if histology is not appropriate) in all but exceptional cases.

Offer cytotoxic chemotherapy for suspected advanced ovarian cancer without a tissue diagnosis (histology or cytology) only:

- In exceptional cases, after discussion at the multidisciplinary team and
- After discussing with the woman the possible benefits and risks of starting chemotherapy without a tissue diagnosis

Methods of Tissue Diagnosis Other Than Laparotomy

If surgery has not been performed, use histology rather than cytology to obtain a tissue diagnosis. To obtain tissue for histology:

- Use percutaneous image-guided biopsy if this is feasible.

- Consider laparoscopic biopsy if percutaneous image-guided biopsy is not feasible or has not produced an adequate sample.

Use cytology if histology is not appropriate.

Management of Suspected Early (Stage I) Ovarian Cancer

The Role of Systematic Retroperitoneal Lymphadenectomy

Perform retroperitoneal lymph node assessment* as part of optimal surgical staging† in women with suspected ovarian cancer whose disease appears to be confined to the ovaries (that is, who appear to have stage I disease).

Do not include systematic retroperitoneal lymphadenectomy (block dissection of lymph nodes from the pelvic side walls to the level of the renal veins) as part of standard surgical treatment in women with suspected ovarian cancer whose disease appears to be confined to the ovaries (that is, who appear to have stage I disease).

*Lymph node assessment involves sampling of retroperitoneal lymphatic tissue from the para-aortic area and pelvic side walls if there is a palpable abnormality, or random sampling if there is no palpable abnormality.

†Optimal surgical staging constitutes: midline laparotomy to allow thorough assessment of the abdomen and pelvis; a total abdominal hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy; biopsies of any peritoneal deposits; random biopsies of the pelvic and abdominal peritoneum; and retroperitoneal lymph node assessment.

Adjuvant Systemic Chemotherapy for Stage I Disease

Do not offer adjuvant chemotherapy to women who have had optimal surgical staging* and have low-risk stage I disease (grade 1 or 2, stage Ia or Ib).

Offer women with high-risk stage I disease (grade 3 or stage Ic) adjuvant chemotherapy consisting of six cycles of carboplatin.

Discuss the possible benefits and side effects of adjuvant chemotherapy with women who have had suboptimal surgical staging* and appear to have stage I disease.

*Optimal surgical staging constitutes: midline laparotomy to allow thorough assessment of the abdomen and pelvis; a total abdominal hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy; biopsies of any peritoneal deposits; random biopsies of the pelvic and abdominal peritoneum; and retroperitoneal lymph node assessment.

Management of Advanced (Stage II–IV) Ovarian Cancer

Note that recommendations 1.1 and 1.2 in NICE technology appraisal guidance 55 ('Guidance on the use of paclitaxel in the treatment of ovarian cancer'; available at www.nice.org.uk/guidance/TA55) are on first-line chemotherapy in the treatment of ovarian cancer.

Primary Surgery

If performing surgery for women with ovarian cancer, whether before chemotherapy or after neoadjuvant chemotherapy, the objective should be complete resection of all macroscopic disease.

Intraperitoneal Chemotherapy

Do not offer intraperitoneal chemotherapy to women with ovarian cancer, except as part of a clinical trial.

Support Needs of Women with Newly Diagnosed Ovarian Cancer

Offer all women with newly diagnosed ovarian cancer information about their disease, including psychosocial and psychosexual issues, that:

- Is available at the time they want it
- Includes the amount of detail that they want and are able to deal with
- Is in a suitable format, including written information

Ensure that information is available about:

- The stage of the disease, treatment options, and prognosis
- How to manage the side effects of both the disease and its treatments in order to maximise wellbeing

- Sexuality and sexual activity
- Fertility and hormone treatment
- Symptoms and signs of disease recurrence
- Genetics, including the chances of family members developing ovarian cancer
- Self-help strategies to optimise independence and coping
- Where to go for support, including support groups
- How to deal with emotions such as sadness, depression, anxiety, and a feeling of a lack of control over the outcome of the disease and treatment

Clinical Algorithm(s)

The following algorithms are available in Appendix C in the original guideline document:

- Overview of pathway
- Detection in primary care
- Tests in secondary care

Scope

Disease/Condition(s)

Ovarian cancer

Guideline Category

Counseling

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Family Practice

Internal Medicine

Obstetrics and Gynecology

Oncology

Radiology

Surgery

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Health Care Providers

Nurses

Patients

Physician Assistants

Physicians

Public Health Departments

Guideline Objective(s)

To provide evidence-based recommendations concerning clinical practice on the recognition and initial management of ovarian cancer

Target Population

Adult women (18 years and older) with:

- Epithelial ovarian cancer
- Fallopian tube carcinoma
- Primary peritoneal carcinoma
- Suspected ovarian or primary peritoneal carcinoma
- Borderline ovarian cancer

Note: The following groups will not be covered:

Children (younger than 18 years) with ovarian malignancy
Women with pseudomyxoma peritonei
Women with relapsed ovarian, fallopian tube, or peritoneal cancer
Women with germ cell tumours of the ovary
Women with sex cord stromal tumours of the ovary
Women with secondary cancers metastasising to the ovary or peritoneum

Interventions and Practices Considered

Assessment/Evaluation

1. Assessment of signs and symptoms
2. Measurement of tumour markers
    - Serum CA125
    - Alpha fetoprotein (AFP)
    - Beta human chorionic gonadotrophin (beta-hCG)
3. Calculation of risk of malignancy index I
4. Imaging studies
    - Ultrasound scan of pelvis and abdomen
    - Computed tomography (CT) scan of pelvis and abdomen
5. Tissue diagnosis
    - Percutaneous image-guided biopsy
    - Laparoscopic biopsy
    - Histological or cytological assessment

Management/Treatment

1. Management of early (stage I) ovarian cancer

    - Retroperitoneal lymph node assessment
    - Adjuvant chemotherapy (carboplatin), as indicated
2. Management of advanced (stage II–IV) ovarian cancer
    - Surgery (before chemotherapy or after neo-adjuvant chemotherapy)
    - Chemotherapy
3. Provision of support and information to patients

Major Outcomes Considered

- Sensitivity and specificity of diagnostic tests
- Survival (overall, 5 year, median, disease free)
- Morbidity
- Mortality
- Number and severity of adverse events
- Quality of life
- Cost effectiveness (quality-adjusted live years)

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre for Cancer on behalf of the National Institute for Health and Clinical Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Developing Clinical Evidence-based Questions

Background

The list of key clinical issues listed in the scope (see the "Description of Methods Used to Formulate the Recommendations" field) were developed in areas that were known to be controversial or uncertain, where there was identifiable practice variation, or where NICE guidelines were likely to have most impact.

Method

From each of the key clinical issues identified in the scope the Guideline Development Group (GDG) formulated a clinical question. For clinical questions about interventions, the patient, information, comparison, outcome (PICO) framework was used. This structured approach divides each question into four components: the population (the population under study – P), the interventions (what is being done – I), the comparisons (other main treatment options – C), and the outcomes (the measures of how effective the interventions have been – O). Where appropriate, the clinical questions were refined once the evidence had been searched and, where necessary, sub-questions were generated. The final list of clinical questions can be found in Appendix 5 of the full version of the original guideline document.

Review of Clinical Literature

Scoping Search

An initial scoping search for published guidelines, systematic reviews, economic evaluations, and ongoing research was carried out on the following databases or websites: National Library for Health (NLH) Guidelines Finder (now NHS Evidence), National Guideline Clearinghouse, Cochrane Database of Systematic Reviews (CDSR), Heath Technology Assessment Database (HTA), National Health Service Economic Evaluations Database (NHSEED), DH Data, Medline, and EMBASE.

At the beginning of the development phase, initial scoping searches were carried out to identify any relevant guidelines (local, national, or international) produced by other groups or institutions.

Developing the Review Protocol

For each clinical question, the information specialist and researcher (with input from other technical team and guideline development group [GDG] members) prepared a review protocol. This protocol explains how the review was to be carried out (see Table A in the full version of the original guideline document; see the "Availability of Companion Documents" field) in order to develop a plan of how to review the evidence, limit the introduction of bias, and for the purposes of reproducibility. All review protocols are available in the full evidence review (see the "Availability of Companion Documents" field).

Searching for the Evidence

In order to answer each question the National Collaborating Centre for Cancer (NCC-C) information specialist developed a search strategy to identify relevant published evidence for both clinical and cost effectiveness. Key words and terms for the search were agreed in collaboration with the GDG. When required, the health economist searched for supplementary papers to inform detailed health economic work (see section on 'Incorporating Health Economic Evidence').

Search filters, such as those to identify systematic reviews and randomised controlled trials (RCTs) were applied to the search strategies when there was a wealth of these types of studies. No language restrictions were applied to the search; however, foreign language papers were not requested or reviewed (unless of particular importance to that question).

The following databases were included in the literature search:

- The Cochrane Library
- Medline and Premedline 1950 onwards
- Excerpta Medica (EMBASE) 1980 onwards
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) 1982 onwards
- Allied & Complementary Medicine (AMED) 1985 onwards
- British Nursing Index (BNI) 1985 onwards
- PsycINFO 1806 onwards
- Web of Science [specifically Science Citation Index Expanded] (SCI-EXPANDED) 1899 onwards and Social Sciences Citation Index (SSCI) 1956 onwards
- Biomed Central 1997 onwards

From this list the information specialist sifted and removed any irrelevant material based on the title or abstract before passing to the researcher. All the remaining articles were then stored in a Reference Manager electronic library.

Searches were updated and re-run 6–8 weeks before the stakeholder consultation, thereby ensuring that the latest relevant published evidence was included in the database. Any evidence published after this date was not included. For the purposes of updating this guideline, 16 July 2010 should be considered the starting point for searching for new evidence.

Further details of the search strategies, including the methodological filters used, are provided in the evidence review (see the "Availability of Companion Documents" field).

Critical Appraisal

From the literature search results database, one researcher scanned the titles and abstracts of every article for each question and full publications were ordered for any studies considered relevant or if there was insufficient information from the title and abstract to inform a decision. When the papers were obtained the researcher applied inclusion/exclusion criteria to select appropriate studies which were then critically appraised.

Incorporating Health Economics Evidence

For each topic that was prioritised for economic analysis a comprehensive systematic review of the economic literature was conducted. Where published economic evaluation studies were identified that addressed the economic issues for a clinical question, these are presented alongside the clinical evidence wherever possible. For those clinical areas reviewed, the information specialists used a similar search strategy as used for the review of clinical evidence but with the inclusion of a health economics filter. Each search strategy was designed to find any applied study estimating the cost or cost effectiveness of the topic under consideration. A health economist reviewed abstracts and relevant papers were ordered for appraisal.

Published economic evidence was obtained from a variety of sources:

- Cochrane HTA
- NHS EED
- Medline
- EMBASE

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Overall Quality of Outcome Evidence in Grading of Recommendations Assessment, Development and Evaluation

Level	Description
High	Further research is very unlikely to change confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
Low	Very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre for Cancer (NCC-C) on behalf of the National Institute for Health and Clinical Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Critical Appraisal

For each question, data on the type of population, intervention, comparator, and outcomes (PICO) were extracted and recorded in evidence tables and an accompanying evidence summary prepared for the Guideline Development Group (GDG) (see evidence review in the "Availability of Companion Documents" field). All evidence was considered carefully by the GDG for accuracy and completeness.

All procedures were fully compliant with National Institute of Health and Clinical Effectiveness (NICE) methodology as detailed in the guidelines manual (NICE 2009; see the "Availability of Companion Documents" field). In general, no formal contact was made with authors; however, there were ad hoc occasions when this was required in order to clarify specific details.

GRADE (Grading of Recommendations, Assessment, Development, and Evaluation)

For interventional questions, studies which matched the inclusion criteria were evaluated and presented using a modification of GRADE (see the

NICE Guidelines Manual; see the "Availability of Companion Documents" field; http://gradeworkinggroup.org/). Where possible this included meta-analysis and synthesis of data into a GRADE 'evidence profile'. The evidence profile shows, for each outcome, an overall assessment of both the quality of the evidence as a whole (low, moderate, or high) as well as an estimate of the size of effect. A narrative summary (evidence statement) was also prepared.

Each topic outcome was examined for the quality elements defined in Table B in the full version of the original guideline document (see the "Availability of Companion Documents" field) and subsequently graded using the quality levels listed in the "Rating Scheme for the Strength of Evidence" field. The reasons for downgrading or upgrading specific outcomes were explained in footnotes in the full version of the original guideline document (see the "Availability of Companion Documents" field).

Incorporating Health Economics Evidence

Prioritising Topics for Economic Analysis

In addition to the review of the relevant clinical evidence, the GDG were required to determine whether or not the cost effectiveness of each of the individual clinical questions should or could be investigated. After the clinical questions were decided, and with the help of the health economist, the GDG agreed which of the clinical questions were an economic priority for analysis. Further details of the economic prioritisation are provided in the evidence review in the full version of the original guideline document see the "Availability of Companion Documents" field). These 'economic priorities' were chosen on the basis of criteria listed in the Methodology section of the full version of the original guideline document, in broad accordance with the 'NICE guidelines manual 2009'.

Overall Relevance of the Topic

- *The number of patients affected*: Interventions affecting relatively large numbers of patients were given a higher economic priority than those affecting fewer patients.
- *The health benefits to the patient*: Interventions that were considered to have a potentially significant impact on both survival and quality of life were given a higher economic priority.
- *The per patient cost*: Interventions with potentially high financial (cost/savings) implications were given high priority compared to interventions expected to have lower financial implications.
- *Likelihood of changing clinical practice*: Priority was given to topics that were considered likely to represent a significant change to existing clinical practice.

Uncertainty

- *High level of existing uncertainty*: Higher economic priority was given to clinical questions in which further economic analysis was considered likely to reduce current uncertainty over cost-effectiveness. Low priority was given to clinical questions when the current literature implied a clearly 'attractive' or 'unattractive' incremental cost-effectiveness ratio, which was regarded as generalisable to a UK healthcare setting.
- *Likelihood of reducing uncertainty with further analyses (feasibility issues)*: When there was poor evidence for the clinical effectiveness of an intervention, then there was considered to be less justification for an economic analysis to be undertaken.

Economic Analysis

Once the priority topics for economic analysis had been agreed by the GDG, the health economist investigated whether or not a cost-effectiveness analysis of each topic could be carried out. Cost-effectiveness evaluations require evidence on numerous parameters, including treatment effects, health-related preferences (utilities), healthcare resource use, and costs. However, high quality evidence on all relevant parameters within an economic analysis is not always available. If the evidence base used to inform a cost-effectiveness analysis is poor, decisions based upon such an analysis may be subject to a high degree of uncertainty and therefore cost effectiveness analysis would not be appropriate.

For those clinical questions where an economic model was required, cost-utility analysis was undertaken using a decision tree approach. Decision tree is an analytical method of evaluating all options and consequences relevant to a specific decision problem. Assumptions and designs of the decision models were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions.

The details of the model are presented in the evidence review and Appendix 1 of the full version of the original guideline document (see the "Availability of Companion Documents" field). During the analysis the following general principles were adhered to:

- The GDG Chair and Clinical Lead were consulted during the construction and interpretation of the analysis.
- The analysis was based on the best evidence from the systematic review.
- Assumptions were reported fully and transparently.

- The results were subject to thorough sensitivity analysis and limitations discussed.
- Costs were calculated from a health services perspective.

Methods Used to Formulate the Recommendations

Expert Consensus

Informal Consensus

Description of Methods Used to Formulate the Recommendations

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre for Cancer (NCC-C) on behalf of the National Institute for Health and Clinical Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

The Guideline Development Group

The ovarian cancer GDG was recruited in line with the 'NICE guidelines manual' (NICE 2009). The first step was to appoint a Chair and a Lead Clinician. Advertisements were placed for both posts and candidates were interviewed before being offered the role. The NCC-C Director, GDG Chair and Lead Clinician identified a list of specialties that needed to be represented on the GDG. Requests for applications were sent to the main stakeholder organisations, cancer networks and patient organisations/charities (see Appendix 6.2 of the full version of the original guideline). Individual GDG members were selected by the NCC-C Director, GDG Chair and Lead Clinician, based on their application forms. The guideline development process was supported by staff from the NCC-C, who undertook the clinical and health economics literature searches, reviewed and presented the evidence to the GDG, managed the process and contributed to drafting the guideline.

Guideline Development Group Meetings

Eleven GDG meetings were held between 27 April 2009 and 20 July 2010. During each GDG meeting (either held over one or two days) clinical questions and clinical and economic evidence were reviewed, assessed, and recommendations formulated. At each meeting patient/carer and service-user concerns were routinely discussed as part of a standing agenda item.

NCC-C project managers divided the GDG workload by allocating specific clinical questions, relevant to their area of clinical practice, to small sub-groups of the GDG in order to simplify and speed up the guideline development process. These groups considered the evidence, as reviewed by the researcher, and synthesised it into draft recommendations before presenting it to the GDG as a whole. Each clinical question was led by a GDG member with expert knowledge of the clinical area (usually one of the healthcare professionals). The GDG subgroups often helped refine the clinical questions and the clinical definitions of treatments. They also assisted the NCC-C team in drafting the section of the guideline relevant to their specific topic.

Patient/Carer Members

Individuals with direct experience of ovarian cancer gave an important user focus to the GDG and the guideline development process. The GDG included three patient/carer members. They contributed as full GDG members to writing the clinical questions, helping to ensure that the evidence addressed their views and preferences, highlighting sensitive issues and terminology relevant to the guideline, and bringing service-user research to the attention of the GDG.

Needs Assessment

As part of the guideline development process the NCC-C invited a specialist registrar, with the support of the guideline development group (GDG), to undertake a needs assessment (see Appendix 6.3 of the full version of the original guideline document). The needs assessment aims to describe the burden of disease and current service provision for patients with ovarian cancer in England and Wales, which informed the development of the guideline.

Assessment of the effectiveness of interventions is not included in the needs assessment, and was undertaken separately by researchers in the NCC-C as part of the guideline development process.

The information included in the needs assessment document was presented to the GDG. Most of the information was presented in the early stages of guideline development, and other information was included to meet the evolving information needs of the GDG during the course of guideline development.

The Scope

The remit was translated into a scope document by the GDG Chair and Lead Clinician and staff at the NCC-C in accordance with processes established by the 'NICE guidelines manual 2009'. The purpose of the scope was to:

- Set the boundaries of the development work and provide a clear framework to enable work to stay within the priorities agreed by NICE and the NCC-C and the remit set by the Department of Health
- Inform professionals and the public about the expected content of the guideline.
- Provide an overview of the population and healthcare settings the guideline would include and exclude
- Specify the key clinical issues that will be covered by the guideline
- Inform the development of the clinical questions and search strategy

The scope was subject to a four week stakeholder consultation in accordance with processes established by NICE in the 'NICE guidelines manual 2009'. The full scope is shown in Appendix 4 of the full version of the original guideline document. During the consultation period, the scope was posted on the NICE website (www.nice.org.uk). Comments were invited from registered stakeholder organisations and the NICE Guideline Review Panel. Further information about the Guideline Review Panel can also be found on the NICE website. The NCC-C and NICE reviewed the scope in light of comments received, and the revised scope was reviewed by the Guideline Review Panel, signed off by NICE and posted on the NICE website.

Agreeing the Recommendations

For each clinical question the GDG were presented with a summary of the clinical evidence, and where appropriate economic evidence, derived from the studies reviewed and appraised. From this information the GDG were able to derive the guideline recommendations. The link between the evidence and the view of the GDG in making each recommendation is made explicit in the accompanying LETR (Linking Evidence to Recommendations) statement.

LETR Statements

As clinical guidelines were previously formatted, there was limited scope for expressing how and why a GDG made a particular recommendation from the evidence of clinical and cost effectiveness. To make this process more transparent to the reader, NICE have introduced an explicit, easily understood, and consistent way of expressing the reasons for making each recommendation. This is known as the 'LETR statement' and will usually cover the following key points:

- The relative value placed on the outcomes considered
- The strength of evidence about benefits and harms for the intervention being considered
- The costs and cost effectiveness of an intervention (if formally assessed by the health economics team)
- The quality of the evidence (see discussion of Grading of Recommendations, Assessment, Development and Evaluation [GRADE] in the "Methods used to Analyze the Evidence" field)
- The degree of consensus within the GDG
- Other considerations – for example equalities issues

Where evidence was weak or lacking the GDG agreed the final recommendations through informal consensus. Shortly before the consultation period, ten key priorities and five key research recommendations were selected by the GDG for implementation and the patient algorithms were agreed. To avoid giving the impression that higher grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A Cost-Utility Analysis of Diagnostic Investigations in Primary Care for Women with Symptoms of Ovarian Cancer

The aim of this study was to assess the cost-effectiveness of diagnostic strategies for women presenting with symptoms suggestive of ovarian cancer in primary care. A cost-utility analysis was undertaken to estimate the incremental cost per quality-adjusted life year (QALY) of seven

diagnostic strategies, which included the downstream costs and consequences of subsequent treatments considered likely to reflect current UK clinical practice and to be consistent with recommendations made within this guideline.

Given the various structural and parameter-related assumptions, the base-case results suggest that serum cancer antigen 125 (CA125) is the most cost-effective test. Indeed the results indicate that the serum CA125 diagnostic strategy dominates all other strategies, that is, it is less costly and more effective than at least one other option. The robustness of the model was tested using one-way sensitivity analysis. The results of the deterministic sensitivity analysis showed that although expected costs and health outcomes varied across strategies, the overall ranking of the cost-effective strategy did not change. Moreover, probabilistic sensitivity analysis (PSA) was undertaken to fully assess the effects of the parameter uncertainty on the results. The results of the PSA showed serum CA125 as the dominating strategy and the corresponding cost-effectiveness acceptability curve (CEAC) shows that, at a threshold of £20,000 per QALY, the probability that the serum CA125 strategy is the most cost effective option is almost 73%.

There are a number of limitations to this analysis. The sensitivity analyses conducted were aimed at assessing only parameter uncertainty; however given the complexity of the downstream consequences associated with each strategy further analysis of the later structural assumptions would be beneficial. The costs used were often proxies for costs that were hard to capture and may not fully capture the differences between the different diagnostic strategies, for instance the costs of pelvic examination. Moreover, in the absence of suitable data, the individual test results were assumed to be independent of each other, when in reality this is unlikely. However, the implication of this in terms of the relative cost effectiveness of each of the (combination) tests is unclear.

See Appendix 1 of the full version of the original guideline document for additional detail on the cost analysis.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Consultation and Validation of the Guideline

The draft of the guideline was prepared by National Collaborating Centre for Cancer (NCC-C) staff in partnership with the Guideline Development Group (GDG) Chair and Lead Clinician. This was then discussed and agreed with the GDG and subsequently forwarded to the National Institute for Clinical Excellence (NICE) for consultation with stakeholders.

Registered stakeholders (see Appendix 6.2 in the full version of the original guideline) had one opportunity to comment on the draft guideline which was posted on the NICE website between 24 September 2010 and 19 November 2010 in line with NICE methodology (Guidelines Manual 2009). The Guideline Review Panel also reviewed the guideline and checked that stakeholder comments had been addressed.

The Pre-publication Check Process

Following stakeholder consultation and subsequent revision, the draft guideline was then subject to a pre-publication check (Guidelines Manual 2009). The pre-publication check provides registered stakeholders with the opportunity to raise any concerns about factual errors and inaccuracies that may exist in the revised guideline after consultation.

During the pre-publication check the full guideline was posted on the NICE website for 15 working days, together with the guideline consultation table that listed comments received during consultation from stakeholders and responses from the NCC-C and GDG.

All stakeholders were invited to report factual errors using a standard proforma. NICE, the NCC and the GDG Chair and Lead Clinician considered the reported errors and responded only to those related to factual errors. A list of all corrected errors and the revised guideline were submitted to NICE, and the revised guideline was then signed off by Guidance Executive. The list of reported errors from the pre-publication check and the responses from the NCC-C were subsequently published on the NICE website.

The final document was then submitted to NICE for publication on their website.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate recognition and initial management of ovarian cancer which may result in decreased morbidity and mortality

Potential Harms

- The trade off in adopting a sequential strategy for suspicion of ovarian cancer as recommended means that some women with ovarian cancer would be missed in the first instance. It also was recognised that there would be an impact on health service resources and women tested due to the low prevalence of ovarian cancer in the symptomatic patient group.
- There are a range of methods of obtaining a tissue diagnosis including needle biopsy, laparoscopy, or open laparotomy. All are invasive and therefore carry risks. In addition, attempts at tissue diagnosis are not always successful and this may delay the start of treatment.
- Percutaneous core biopsy was associated with minor local bruising and discomfort.
- There was no direct evidence about the harms of diagnostic laparoscopy or laparotomy in women with suspected advanced ovarian cancer due to receive chemotherapy. Indirect evidence comes from studies reporting diagnostic laparoscopy in patients with ascites of unknown origin. Minor complications were reported in less than two percent of laparoscopies. Major complications occurred at a rate of less than one percent.
- Image-guided biopsy is associated with minor complications, such as local bruising and discomfort. Targeting of the abnormality for biopsy is limited by the imaging technique used and the samples are much smaller, reducing the diagnostic yield. This potentially results in a lower success rate requiring a repeat procedure or surgical biopsy.
- Tissue biopsy by laparoscopy is associated with both major and minor complications, with higher associated major complication rates than image-guided biopsy.
- Both image-guided and laparoscopy biopsy techniques have the potential to damage the abdomino-pelvic organs which may be displaced or tethered to abnormal positions by tumour, fibrosis, or inflammation. There is also a potential risk of tumour being deposited along the biopsy needle track or implanted into the laparoscopic surgery sites.
- Systematic retroperitoneal lymphadenectomy is a major surgical procedure which carries the potential risks of prolonged anaesthesia and surgical complications such as increased blood loss and transfusion, ureteric injury, lymphoedema, lymphocysts, damage to nerves, and major vessels. In addition to concerns about morbidity, there are resource implications.
- A research study compared six versus three cycles of adjuvant carboplatin and paclitaxel in women with early stage ovarian cancer. The higher number of treatment cycles was associated with significantly increased morbidity.
- A Cochrane review of chemotherapy versus surgery for the initial treatment of advanced ovarian cancer. The authors identified only one small randomised controlled trial which had randomised 85 women to receive either one cycle of chemotherapy followed by embolisation of the ovarian artery, debulking surgery and adjuvant chemotherapy, or debulking surgery and adjuvant chemotherapy only. The chemo-embolisation arm did experience less surgery related morbidity.

Qualifying Statements

Qualifying Statements

- This guidance represents the view of the National Institute of Health and Clinical Excellence (NICE), which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer, and informed by the summary of product characteristics of any drugs they are considering.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded

that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

The National Institute for Health and Clinical Excellence (NICE) has developed tools to help organisations implement this guidance. These are available on the NICE Web site (http://guidance.nice.org.uk/CG122).

Key Priorities for Implementation

The following recommendations have been identified as priorities for implementation.

Awareness of Symptoms and Signs

- Carry out tests in primary care (see section 'Asking the right question – first tests' in the "Major Recommendations" field) if a woman (especially if 50 or over) reports having any of the following symptoms on a persistent or frequent basis – particularly more than 12 times per month. See also Referral guidelines for suspected cancer (NICE clinical guideline 27) for recommendations about the support and information needs of people with suspected cancer):
  - Persistent abdominal distension (women often refer to this as 'bloating')
  - Feeling full (early satiety) and/or loss of appetite
  - Pelvic or abdominal pain
  - Increased urinary urgency and/or frequency
- Carry out appropriate tests for ovarian cancer (see section 'Asking the right question – first tests' in the "Major Recommendations" field) in any woman of 50 or over who has experienced symptoms within the last 12 months that suggest irritable bowel syndrome (IBS), because IBS rarely presents for the first time in women of this age. (See the National Guideline Clearinghouse [NGC] summary of the NICE guideline Irritable bowel syndrome in adults: diagnosis and management of irritable bowel syndrome in primary care (NICE clinical guideline 61).

Asking the Right Question – First Tests

- Measure serum cancer antigen 125 (CA125) in primary care in women with symptoms that suggest ovarian cancer (see section 'Awareness of symptoms and signs' in the "Major Recommendations" field).
- If serum CA125 is 35 IU/ml or greater, arrange an ultrasound scan of the abdomen and pelvis
- For any woman who has normal serum CA125 (less than 35 IU/ml), or CA125 of 35 IU/ml or greater but a normal ultrasound:
  - Assess her carefully for other clinical causes of her symptoms and investigate if appropriate.
  - If no other clinical cause is apparent, advise her to return to her general practitioner if her symptoms become more frequent and/or persistent.

Malignancy Indices

- Calculate a risk of malignancy index I (RMI I) score (after performing an ultrasound) and refer all women with an RMI I score of 250 or greater to a specialist multidisciplinary team.

Tissue Diagnosis

- If offering cytotoxic chemotherapy to women with suspected advanced ovarian cancer, first obtain a confirmed tissue diagnosis by histology (or by cytology if histology is not appropriate) in all but exceptional cases.

The Role of Systematic Retroperitoneal Lymphadenectomy

- Do not include systematic retroperitoneal lymphadenectomy (block dissection of lymph nodes from the pelvic side walls to the level of the renal veins) as part of standard surgical treatment in women with suspected ovarian cancer whose disease appears to be confined to the ovaries (that is, who appear to have stage I disease).

Adjuvant Systemic Chemotherapy for Stage I Disease

- Do not offer adjuvant chemotherapy to women who have had optimal surgical staging and have low-risk stage I disease (grade 1 or 2, stage Ia or 1b).

Support Needs of Women with Newly Diagnosed Ovarian Cancer

- Offer all women with newly diagnosed ovarian cancer information about their disease, including psychosocial and psychosexual issues, that:
  - Is available at the time they want it
  - Includes the amount of detail that they want and are able to deal with
  - Is in a suitable format, including written information

Implementation Tools

Audit Criteria/Indicators

Clinical Algorithm

Foreign Language Translations

Patient Resources

Quick Reference Guides/Physician Guides

Resources

Slide Presentation

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Collaborating Centre for Cancer. Ovarian cancer. The recognition and initial management of ovarian cancer. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011 Apr. 28 p. (Clinical guideline; no. 122).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

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Guideline Developer(s)

National Collaborating Centre for Cancer - National Government Agency [Non-U.S.]

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Guideline Committee

Guideline Development Group

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Financial Disclosures/Conflicts of Interest

At the start of the guideline development process all guideline development group members' interests were recorded on a standard declaration form that covered consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent guideline development group meetings, members declared new, arising conflicts of interest which were always recorded (see Appendix 6.1 of the full version of the original guideline document for details).

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site

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Availability of Companion Documents

The following is available:

- Ovarian cancer. The recognition and initial management of ovarian cancer. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011 Apr. 12 p. (Clinical guideline; no. 122). Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site .
- Ovarian cancer. The recognition and initial management of ovarian cancer. Full guideline. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011 Apr. 148 p. (Clinical guideline; no. 122). Electronic copies: Available in PDF from the NICE Web site .
- Ovarian cancer. The recognition and initial management of ovarian cancer. Evidence review. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011 Apr. 318 p. (Clinical guideline; no. 122). Electronic copies: Available in PDF from the NICE Web site .
- Ovarian cancer. NICE pathway. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011 Apr. Various pages. (Clinical guideline; no. 122). Electronic copies: Available from the NICE Web site .
- Ovarian cancer. The recognition and initial management of ovarian cancer. Costing statement. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011 Apr. 8 p. (Clinical guideline; no. 122). Electronic copies: Available in PDF from the NICE Web site .
- Ovarian cancer. The recognition and initial management of ovarian cancer. Clinical audit tools. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011 Apr. (Clinical guideline; no. 122). Electronic copies: Available from the NICE Web site .
- Ovarian cancer. Clinical case scenarios for primary care. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011 Apr. 22 p. (Clinical guideline; no. 122). Electronic copies: Available in PDF from the NICE Web site .
- Ovarian cancer. Clinical case scenarios for primary care. Slide set. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011 Apr. 20 p. (Clinical guideline; no. 122). Electronic copies: Available from the NICE Web site .
- Ovarian cancer. Slide set. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011 Apr. 28 p. (Clinical guideline; no. 122). Electronic copies: Available from the NICE Web site .
- Ovarian cancer. Baseline assessment tool. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011 Apr. (Clinical guideline; no. 122). Electronic copies: Available from the NICE Web site .
- Ovarian cancer GP podcast. Available from the NICE Web site .
- Ovarian cancer SRL podcast. Available from the NICE Web site .
- The guidelines manual 2009. London (UK): National Institute for Health and Clinical Excellence (NICE); 2009 Jan. Electronic copies: Available in PDF from the NICE Archive Web site .

Patient Resources

The following is available:

- Recognition and initial treatment of ovarian cancer. Understanding NICE guidance. Information for people who use NHS services. London: National Institute for Health and Clinical Excellence (NICE); 2011 Apr. 20 p. Electronic copies: Available from the National Institute for Health and Clinical Excellence (NICE) Web site . Also available in Welsh from the NICE Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This summary was completed by ECRI Institute on March 16, 2012.

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